SACHRP Recommendation on Applicability of FDA Regulations
for IRBs (21 CFR 56) and Informed Consent (21 CFR 50)

INTRODUCTION

The HHS regulations regarding human subject protection at 45 CFR 46 differ in limited but significant ways from the FDA regulations regarding human subject protection at 21 CFR 50 and 56. When a research activity is governed by both sets of regulations, then there are certain regulatory provisions that are allowable under 45 CFR 46 that are not allowable under 21 CFR 50 and 56, and thus cannot be applied to the research. The most commonly encountered of these regulatory provisions are the application of the exempt research categories at 45 CFR 46.101(b)(1) through (b)(6), the provision for waiver of consent at 45 CFR 46.116(d), and the provision for a waiver of documentation of consent found at 45 CFR 46.117(c)(1). There is considerable difference in opinion and practice among IRBs, investigators, institutions and sponsors as to when the FDA regulations apply to a research project. To use a common example, an investigator wishes to conduct a retrospective record review of medical records to determine whether drug X had a better outcome than drug Y for arthritis. Some IRBs will consider this to be non-FDA regulated research that is exempt from IRB review and informed consent based on HHS regulation 45 CFR 46.101(b)(4). Other IRBs will consider this to be non-FDA regulated research that needs IRB review but qualifies for a waiver of consent. Finally, a third set of IRBs will determine that this is an FDA regulated clinical investigation that requires IRB review and informed consent under 21 CFR Parts 50 and 56. This is not uncommon, and there are many such examples, as discussed below. OHRP maintains a registration system for IRBs that conduct either HHS funded or supported research or FDA regulated research. If an IRB reviews both types of research, then it must register with both agencies using that system. As of February 3, 2012, there are 2,308 IRBs that are registered with both OHRP and FDA. All of these IRBs face this issue of determining regulatory applicability on a regular basis.

Therefore, SACHRP recommends the issuance of guidance that will provide regulated parties with objective criteria for determining when a research project is under FDA jurisdiction. As represented in the Venn diagram in Appendix II of this recommendation, the goal of this guidance is to clarify the bottom intersecting line, which represents the overlap between FDA and HHS jurisdiction.

OHRP has existing guidance that outlines the steps of analysis as to the level of IRB oversight required of research (http://www.hhs.gov/ohrp/policy/checklists/decisioncharts.html). In summary, that guidance states that the proper analysis under the HHS regulations is:

- Is the activity research?
- Is the activity research involving human subjects?
- Is the activity research that is exempt under 45 CFR 46.101(b)(1) through (6)?
- Is the activity research that can be reviewed through expedited procedures?
- Is the activity research that requires review by a convened IRB?

However, much research is also potentially under FDA jurisdiction. Thus, IRBs could use similar guidance from FDA regarding the definitions of clinical investigation and human subject under the FDA regulations. Ideally, this guidance could be combined with current OHRP guidance on how to determine the status of research under the Common Rule, so that the many IRBs that are registered with both OHRP and FDA would have a single source of guidance on this difficult issue. The result of such guidance would be increased consistency among IRBs and other regulated parties, and subsequently reduced administrative burden on the research community. In addition, if HHS moves forward with the implementation of a Notice of Proposed Rule Making (NPRM) to change the human subject protection regulations, this guidance will provide important public input to OHRP and FDA to proactively consider the relationship between the two sets of regulations and provide clarity on these and similar issues of inconsistency that arise.

RESOLUTION THROUGH GUIDANCE CLARIFYING REGULATORY DEFINITIONS

SACHRP believes that the source of much of the variability of interpretation of the applicability of the FDA regulations stems from the fact that FDA regulations for informed consent (21 CFR Part 50), IRBs (21 CFR Part 56), investigational drugs (21 CFR Part 312), and investigational devices (21 CFR Part 812) contain three different definitions of "human subject," four different definitions of "clinical investigation," and four different definitions of "study article" or its equivalent. These different definitions are provided in Appendix I. It is unclear to the regulated community how to interpret these different definitions, to whom each definition applies, and how the different definitions interact. For instance, it is not clear whether the definitions of "clinical investigation" in 21 CFR Part 50 and 56 are narrower or broader in scope than those in Parts 312 and 812, and when each definition is applicable.

Because these different definitions exist within the FDA regulations, it is difficult to use the same pattern for an algorithm of when the FDA regulations apply. Such an algorithm would follow this order:

- Is the activity a clinical investigation?
- Is the activity a clinical investigation involving human subjects?
- Is the activity exempt under 21 CFR 56.104(a) through (d)?
- Is the activity a clinical investigation that can be reviewed through expedited procedures?
- Is the activity a clinical investigation that requires review by a convened IRB?

If FDA were able to create and publicize an algorithm of this nature, it would resolve many of the issues noted above. SACHRP offers the following thoughts on this issue.

FDA should clarify the interpretation of "clinical investigation" based on the regulatory definitions found in 21 CFR 50, 21 CFR 56, 21 CFR 312, and 21 CFR 812. Each of these four regulations provides a different definition, and it would be very useful to the regulated community if FDA would provide guidance on how these definitions should be interpreted used vis a vis each other and as a whole.[1]

SACHRP notes that the definition of a clinical investigation in 21 CFR Part 56 appears to be the broadest of the four definitions. FDA may find it useful to clarify that Part 56 is the broadest of the definitions and encompasses the other three definitions, and then use it as a platform to provide guidance to the regulated community on the definition of a clinical investigation. For instance, the definition of the term "clinical investigation" in Part 56 says it is an experiment in the broadest sense, and that it is synonymous with terms research, clinical research, clinical study, study, and clinical investigation. Therefore, these terms cannot readily be used to differentiate whether an activity is or is not regulated by FDA under 21 CFR Part 56. FDA may find it useful to clarify this point if in fact there are relevant distinctions between the terms that the regulated community could use to determine whether a given research activity is under FDA jurisdiction.

Two additional criteria in 21 CFR Part 56 that appear critical in determining whether a clinical investigation is regulated by FDA is that the clinical investigation is 1) subject to requirements for prior submission to the FDA under section 505(i) or 520(g) of the Food Drug and Cosmetic Act or 2) the clinical investigation is not subject to requirements for prior submission to the FDA under these sections of the Food, Drug and Cosmetic Act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit. It appears that if the investigator or sponsor must submit the data to FDA, or intends to submit the data to FDA, or FDA might inspect the data, then the clinical investigation (research, study, etc) is regulated by FDA under 21 CFR 56. The "held for inspection" condition seems to be particularly broad and the field would benefit from clarification of this and the other criteria.

FDA should clarify the definition of the terms "involves" and "involving" as they are used in the four definitions of a clinical investigation. FDA could clarify whether a test article has to be

[1] As a model, FDA may wish to consider the May 2011 FDA Draft Guidance for Clinical Investigators, Industry, and FDA Staff on Financial Disclosure by Clinical Investigators, in which the FDA included in the FAQ section questions such as: "How does the definition of 'clinical investigator' in the financial disclosure regulation (21 CFR part 54) relate to the definition in the IND regulations (21 CFR part 312)?" and "How does the definition of 'clinical investigator' in the financial disclosure regulation (21 CFR part 54) relate to the definition in the medical device regulations (21 CFR part 812)?" This type of comparison is very useful.

physically used in the research activity for it to be considered an FDA regulated clinical investigation, or whether alternatively the study can "involve" a test article merely by studying existing data, such as medical records, about the use of the product. This point would help to clarify whether retrospective medical records reviews should be considered to be FDA regulated clinical investigations.

Another difference between the definitions is that under 21 CFR Part 312 any use of a drug, except for the use of a marketed drug in the course of medical practice, is a clinical investigation. However, under 21 CFR Part 812 there is only a clinical investigation when the purpose is to study the safety or effectiveness of the device. FDA should clarify how these two different definitions should be interpreted, particularly as they interact with the definitions of "clinical investigation" in 21 CFR Parts 50 and 56.

In order to provide FDA with a starting point in considering this approach, SACHRP provides the following recommendations on the interpretation of the regulatory definitions:

1. FDA should issue guidance stating that the definition of a clinical investigation at 21 CFR Part 56.102(c) is the broadest statement of FDA's interpretation of a clinical investigation, and encompasses the definitions of a clinical investigation in Parts 50, 312, and 812. As such, IRBs and investigators should use the definition in Part 56 for determinations of whether a given project meets the definition of a clinical investigation.

2. FDA should clarify that even though Part 56 states that "The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part," in fact the definition of research at 45 CFR 46.102(d) is a completely distinct regulatory definition that is not synonymous with the definition of a clinical investigation.

3. FDA should clarify the clause in 21 CFR Part 56.102(c) that states that a clinical investigation, "either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit." FDA should clarify whether this clause causes retrospective record reviews, interviews and questionnaires to become FDA regulated clinical investigations if the intent is to submit the data to FDA or hold the data for FDA inspection. SACHRP recommends that FDA clarify that retrospective record reviews, even when regarding the safety and efficacy of a study article, do not qualify as FDA-regulated clinical investigations. If FDA were to interpret the definition of a clinical

investigation such that any retrospective records review involving a regulated study article is a clinical investigation, and therefore that consent is required, much research would not be possible to conduct due to the inability to obtain consent, and the creation of medical knowledge would be significantly curtailed.

4. FDA should clarify the definitions of the terms "involves" and "involving," as they are used in the definition of a clinical investigation in 21 CFR Part 56, related to whether the data will be submitted to FDA or held for FDA inspection, as described in the recommendation above.

5. FDA should clarify whether the definition of human subject should include consideration of whether or not the data are identifiable. If a link is not maintained, or there is only a one-way link, then perhaps the humans would not be subjects under the FDA definition of a human subject. If a link is maintained, at what point do they become human subjects under the FDA definitions?

6. Finally, we believe that FDA should further publicize that the definition of "human subject" is limited to living individuals, and does not include dead individuals. The recent March 2011, FDA guidance entitled "Exception from Informed Consent Requirements for Emergency Research" clarified this issue, but if FDA provides guidance on the definition of a clinical investigation, it would also be a practical location to provide better public visibility of this FDA interpretation.

RESOLUTION THROUGH GUIDANCE ON SPECIFIC ISSUES

As an alternate approach to issuing guidance clarifying the regulatory definitions of clinical investigation, human subject, and study article, as discussed above, FDA may find it more practical and useful to issue guidance on specific examples instead. SACHRP therefore provides the following specific issues and cases that cause confusion as to whether they are FDA regulated clinical investigations.

Retrospective Record Reviews

There is great diversity of opinion among the regulated community as to whether retrospective records reviews are or are not FDA regulated clinical investigations. These retrospective reviews can involve a variety of source data, such as patients' medical records, insurance company records, and publicly available sources such as the Centers for Disease Control (CDC) Death Index. Depending on how the data is collected and recorded, such research may qualify as exempt from the requirements of 45 CFR 46 under the exemption at 46.102(b)(4), may qualify as research not including human subjects under the OHRP "Guidance on Research Involving Coded

Private Information or Biological Specimens," or may qualify for a waiver of informed consent under 45 CFR 46.116(d). However, if the research qualifies as an FDA regulated clinical investigation, then IRB review is required and consent cannot be waived. The practical effect of applying FDA jurisdiction to these studies means that many of them would become impossible or impractical to conduct due to the requirement for informed consent. FDA should issue guidance clarifying whether, and if so, under what circumstances retrospective record reviews qualify as FDA regulated clinical investigations.

SACHRP provides the following recommendation:

1. FDA should issue guidance clarifying when, if ever, retrospective record reviews qualify as an FDA-regulated clinical investigation. SACHRP recommends that FDA clarify that retrospective record reviews, even when regarding the safety and efficacy of a study article, do not qualify as FDA-regulated clinical investigations. The guidance should supply a clear rationale so that regulated entities can apply that rationale to specific cases. Furthermore, SACHRP recommends that FDA establish a standard that strikes the best balance for the public good by promoting the discovery and availability of useful medical knowledge while to the extent necessary providing FDA with control over claims of safety and efficacy of FDA regulated products.

Collection of Data for Purposes other than Establishing Safety and Efficacy of Products

FDA should clarify when the use of data generated as part of medical practice is a "clinical investigation." For example, institutions and physicians often implement quality improvement activities that are intended to improve the quality of patient care, and collect patient or provider data regarding the implementation of the practice for clinical, cost analysis, or administrative purposes. FDA should clarify whether such activities could ever qualify as clinical investigations, and if so, what the determining criteria would be.

SACHRP provides the following recommendation:

1. FDA should issue guidance clarifying that collecting or using medical data for purposes other than establishing the safety and efficacy of test articles is not an FDA regulated activity. Examples provided by FDA should include cost effectiveness and quality improvement.

Drug and Device Registries

FDA should provide guidance clarifying when, if ever, drug and device registries qualify as FDA-regulated clinical investigations, and provide the relevant criteria that cause a registry to be

FDA regulated. Possible criteria that might be addressed include the identity of the individual or entity that establishes and maintains the registry. The guidance should supply a clear rationale so that regulated entities can apply that rationale to specific cases.

SACHRP provides the following recommendation:

1. FDA should issue guidance clarifying whether prospective registries used to collect data regarding the safety and efficacy of FDA regulated test articles are FDA regulated clinical investigations, particularly when the study article is not prescribed or used as a result of the existence of the registry. FDA should consider whether certain types of registries, such as registries designed to collect data on fetal exposure to approved drugs through the mother's use during pregnancy, in which the data is collected through voluntary reporting by the physician or the mother, should be considered FDA-regulated clinical investigations, as this data collection cannot be effectively conducted under FDA regulations due to the difficulty of obtaining informed consent.

Risk Evaluation and Mitigation Strategies

FDA should provide guidance clarifying whether and when risk evaluation and mitigation strategies qualify as FDA regulated clinical investigations. [AJ will state the problem]

SACHRP provides the following recommendation:

FDA should issue guidance clarifying that risk evaluation and mitigation strategies are not FDA regulated clinical investigations, unless the study article is prescribed or used as a result of the existence of the risk evaluation and mitigation strategy.

Training Activities

Training activities also often raise questions of FDA jurisdiction. These training activities may involve medical providers or subjects. It would be useful if FDA provided guidance regarding various training activities clarifying whether or not FDA considers the training activities to be clinical investigations:

a. Research to evaluate the effects of training on the administration or use of test articles such as drugs and devices.
b. Training activities regarding regulated products that are mandated by FDA.
c. Training on how to use a device or drug.

SACHRP provides the following recommendation:

FDA should issue guidance clarifying that training activities that are conducted as part of an FDA regulated clinical investigation fall within the FDA regulated investigation. However, training activities that occur separately from an FDA regulated clinical investigation are not, in and of themselves, a clinical investigation unless they involve use of a test article, a human subject, and data are going to be submitted to FDA or held for FDA. Therefore, an IRB can apply the exemption at 45 CFR 46.102(b) to such training activities if appropriate.

Interviews and Questionnaires

FDA should issue guidance on whether interviews and questionnaires that are administered to medical providers and subjects are FDA regulated clinical trials when they are separate from a clinical investigation. When interviews and questionnaires are administered as part of clinical investigation, they fall within the scope of that investigation. However, sponsors or other parties at times wish to administer interviews or questionnaires separately from a clinical investigation.

SACHRP provides the following recommendation:

FDA should issue guidance clarifying that interviews and questionnaires that are administered to medical providers and subjects separate from FDA regulated clinical trials are not by themselves FDA regulated clinical investigations unless the interview/questionnaire also involves the use of the test article, a human subject, and the data will be submitted to FDA or held for FDA inspection. Therefore, an IRB can apply the exemptions at 45 CFR 46.102(b) to such interviews and questionnaires if appropriate.

Studies of Surgical Techniques

An issue of confusion among IRBs is the applicability of FDA regulations to studies of surgical techniques. It is commonly stated that FDA does not regulate surgery, including in FDA's guidance entitled "Available Therapy," which states, "Some confusion has arisen regarding whether available therapy refers only to products approved by FDA for the use in question, or whether the term could also refer to products used off-label or to treatments not regulated by FDA, such as surgery."[2] FDA should clarify when a study of a surgical technique is or is not a device study. Because all surgery involves the use of at least one, and often dozens, of devices, it is either the case that all research on surgical techniques is FDA-regulated device research, or there is some criteria by which some research on surgical techniques does not qualify as device research. Also, if FDA determines that some or all research on surgical techniques does qualify as device research, it would be helpful if FDA guidance provided criteria for determining which devices being used in a given study of surgical technique are the devices for which the IRB must make appropriate regulatory device findings. Surgery often involves dozens of devices, including oximeters, scalpels, sutures, chest spreaders, heart-lung bypass, IV pumps, etc. It

[2] online at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126586.htm:

would be burdensome for IRBs and investigators to collect the labeling for each of these devices to determine the regulatory status, particularly in multi-site studies because different investigators would very often be using different oximeters, scalpels, etc.

SACHRP provides the following recommendations:

FDA should issue guidance clarifying that studies of surgical techniques are only clinical investigations of devices when the study evaluates the safety or efficacy of the device. If the study is only to test the new technique and not the device, then it falls outside of the device regulations.

Studies of Devices Intended to Obtain Physiologic Data as Opposed to Information About the Safety and Efficacy of the Device

FDA should clarify that the use of a medical device (e.g., an MRI in behavioral and social science research) when the purpose of the study is to obtain basic physiologic information, rather than to test the safety or effectiveness of the device, is not a clinical investigation.

SACHRP provides the following recommendation:

FDA should clarify that the use of a medical device to obtain basic physiologic information, as opposed to obtaining data regarding the safety or effectiveness of the device, is not a clinical investigation.

CONCLUSION

SACHRP considers the issues presented in this recommendation to be very important. The current lack of clarity of the applicability of FDA regulations causes IRBs, investigators, institutions, and sponsors to apply the FDA regulations inconsistently, causes extensive unnecessary administrative burden and regulatory uncertainty, and may place unnecessary restrictions on valuable research. SACHRP hopes that FDA, OHRP, OCR and other agencies that have adopted the Common Rule will work together to enhance the human subject protection system by addressing these issues.

Appendix I

Relevant Regulations

There are four different definitions of clinical investigation found in 21 CFR 50 and 56, 312, and 812:

21 CFR 50.3(c): Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

21 CFR 56.102(c): Clinical investigation means any experiment that involves a test article and one or more human subjects and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part.

21 CFR 312.3(b): Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

21 CFR 812.3(h): Investigation is a clinical investigation or research involving one or more subjects to determine the safety and/or effectiveness of a device.

There are four different definitions of test article (or its equivalent) found in 21 CFR 50 and 56, 312, and 812:

21 CFR 50.3(j): Test article means any drug (including a biological product for human use) medical device for human use, human food additive, color additive, electronic product, or any

other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.

21 CFR 56.102(l): Test article means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.

21 CFR 312.3(b): Investigational new drug means a new drug, antibiotic drug, or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous for purposes of this part.

21 CCFR 812.3(g): Investigational device means a device, including a transitional device, that is the object of an investigation.

<u>There are three different definitions of human subject found in 21 CFR 50 and 56, 312, and 812.</u>

21 CFR 50.3(g) and 56.102(e): Human subject means an individual who is or becomes a participant in research, either as a recipient of the test articles or as a control. A subject may be either a healthy human or a patient.

21 CFR 312.3(b): Human subject means a human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease.

21 CFR 812.3(p): Subject means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control A subject may be in normal health or may have a medical condition or disease.

Appendix II